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GOVERNMENT OF INDIA
PATENT OFFICE BRANCH
MUNICIPAL MARKET BUILDING
LEIRD FLOOR, KAROL BAGH,
NEW DELHI-110 005.

REC'D 15 FEB 2001
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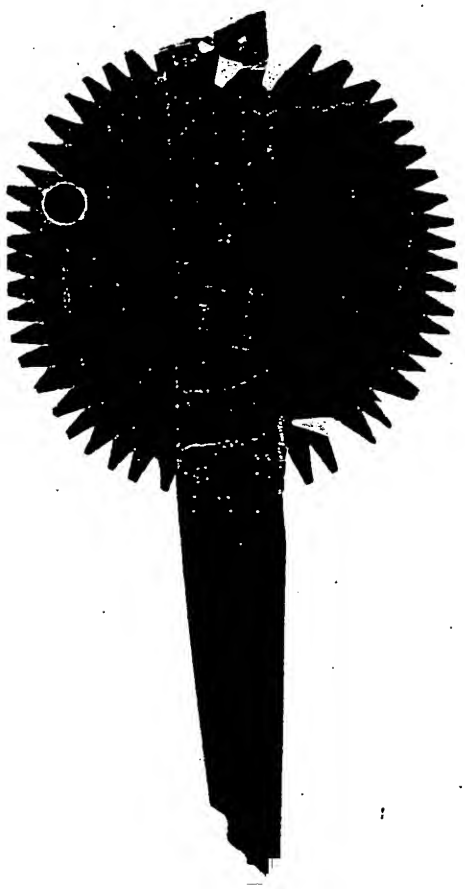
I the undersigned being an officer duly authorised in accordance with the provision of the Patent Act, 1970 hereby certify that annexed hereto is a true copy of the application form and the Complete specification filed in connection with Patent Application No. 1297/Del/99 dated 28.9.99.

Witness my hand this 20th day of September, 2000

(H.C. BAKSHI)
DEPUTY CONTROLLER OF PATENTS & DESIGNS.



1297/Del/99
28/9/99

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT
(See Sections 7 ,54 and 135)

We **PANACEA BIOTEC LIMITED** of the address: 102 Ashok Plaza, 24 School Lane, New Delhi -110001 India, an Indian Company Registered under the Companies Act 1956,

hereby declare -

(a) that we are in possession of an invention titled-

"Controlled Release Composition Comprising Nimesulide"

(b) that the Provisional specification relating to this invention is filed with this Application.

(c) that there is no lawful ground of objection to the grant of a Patent to us.

We **PANACEA BIOTEC LIMITED** of the address: 102 Ashok Plaza, 24 School Lane, New Delhi -110001 India, an Indian Company Registered under the Companies Act 1956, further declare that the inventors for the said invention are **Amarjit Singh** of the address 102 Ashok Plaza, 24 School Lane, New Delhi -110001 India and **Rajesh Jain** of the address 102 Ashok Plaza, 24 School Lane, New Delhi -110001 India, all Indian citizens.

That we are the Assignees or legal representatives of **Amarjit Singh** of the address 102 Ashok Plaza, 24 School Lane, New Delhi -110001 India and **Rajesh Jain** of the address 102 Ashok Plaza, 24 School Lane, New Delhi -110001 India, all Indian citizens.

That our address for service in India is as follows:

KAN AND KRISHME, ADVOCATES PATENT AND TRADEMARK ATTORNEYS, B-2 /47 C LAWRENCE ROAD, DELHI-110035, INDIA

Tel: 7153359, 7183693, 7860511 Fax: 7105864

ORIGINAL

That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of Patent to us on this Application.

Following are these attachments with the Application:

(a) Provisional specification in triplicate
(b) Statement and undertaking on Form (3)
(c) Fee Rs. ..... Cheque bearing no. ..... date on .....Bank

We request that a Patent may be granted to us for the said invention.

Dated this 28th day of September 1999.

Sharad Vadehra
of KAN AND KRISHME
ATTORNEY FOR THE APPLICANTS

TO,
THE CONTROLLER OF PATENTS
THE PATENT OFFICE
NEW DELHI

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)
COMPLETE SPECIFICATION
(See Section 10)

"Controlled Release Composition Comprising Nimesulide"

PANACEA BIOTEC LIMITED of the address :102 Ashok Plaza, 24 School Lane, New Delhi – 110001 India, an Indian Company Registered under the Companies Act 1956.

The following specification particularly describes and ascertains the nature of this invention and the manner in which it has to be performed:

Controlled Release Compositions Comprising Nimesulide

The present invention relates to a controlled release composition of Nimesulide. The composition is related to a once-a-day dosage forms which are very useful in treatment of chronic diseases such as arthritis.

TECHNICAL BACKGROUND OF THE INVENTION

Nimesulide is a nonsteroidal anti-inflammatory drug (NSAID) that also has antipyretic and analgesic properties. The compound is weakly acidic (pKa = 6.5) and differs from other NSAIDs in that its chemical structure contains a sulfonanilide moeity as the acidic group. (fig. 1) (Magni E, Nimesulide an overview, Drug Invest 1991; 3 Suppl. 2: 1-3).

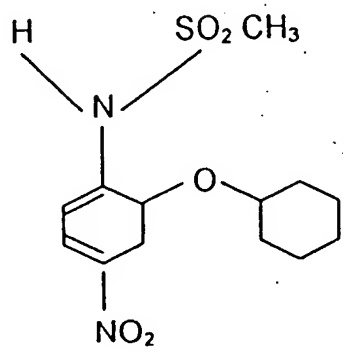


Fig. 1

The therapeutic effects of NSAIDs are largely the result of their ability to inhibit prostaglandin synthesis via inhibition of cyclo-oxygenase. Unfortunately, this effect is also responsible for the inhibition of gastroprotective prostaglandins, which leads to gastrointestinal intolerance.

In vitro, Nimesulide is a relatively weak inhibitor of prostaglandin synthesis and appears to exert its effects through a variety of mechanisms. (Magni E. The effect of nimesulide on prostanoid formation. Drugs 1993; 46 Suppl. 1:10-4.) Indeed, the mechanism of action of this drug is more complex than previously thought and may involve interference with the production/action of mediators other than prostaglandins such as enzymes, toxic oxygen derivatives, cytokines, platelet-activating factor (PAF) and histamine.

The anti-inflammatory, analgesic and antipyretic activities of Nimesulide, a non-steroidal anti-inflammatory drug (NSAID) of the sulfonanilide class, have been demonstrated in a number of experimental models and in numerous clinical trials. Nimesulide has exhibited potency similar to or greater than that of indomethacin, diclofenac, piroxicam and ibuprofen in standard animal models of inflammation such as carrageenin-induced rat paw oedema and inflammation, ultraviolet light-induced erythema in guinea-pigs and adjuvant arthritis in rats. The analgesic potency in nimesulide was similar to that of ibuprofen and less than that of indomethacin in an acetic acid writhing test in rats, and acetic acid and acetycholine writhing tests in mice. Nimesulide has shown superior antipyretic potency to indomethacin, ibuprofen, aspirin and paracetamol (acetaminophen) in rats with yeast-induced fever.

Nimesulide is a relatively weak inhibitor of prostaglandin synthesis in vitro and appears to exert its effects through a variety of mechanisms including free-radical scavenging, effects on histamine release, the neutrophil mycloperoxidase pathway, bradykinin activity, tumour necrosis factor-α

release, cartilage degradation, metalloprotease synthesis, phosphodiesterase type IV inhibition, platelet aggregation and synthesis of platelet activating factor. Animal studies have suggested that Nimesulide is less ulcerogenic than aspirin, indomethacin, naproxen, piroxicam and ibuprofen. Nimesulide appears to have little effect on renal prostaglandin synthesis in rats.

Nimesulide dose dependently (0.3 to 15.4 mg/L) and at near therapeutic plasma drug concentrations affects neutrophil activity in vitro during inflammatory reactions in at least 2 steps of the cell response. It is also reported to inhibit the release of histamine by 50% during immunological reaction in the perfused sensitised guinea pig lung model at 0.93 mg/L level (Berti F, et al., Arzneimittel Forschung 1990; 40: 1011-6). Further, when added to human articular cartilage explant in vitro, nimesulide, at a therapeutic concentration (3 mg/L), reduced the degradation of the matrix by inhibiting the synthesis of metalloproteinases such as collagenase and stromelysin (Pelletier JP, Martel-Pelletier J, Drugs 1993; 46 Suppl. 1: 34-9).

In yeast induced febrile rats, the ED_{50} (producing a 5°C decrease in rectal temperature) of nimesulide is reported to be 0.21 mg/kg, indicating more potency than indomethacin (ED_{50} = 1.8 mg/kg), ibuprofen (ED_{50} = 3.7 mg/kg) and aspirin (ED_{50} = 25 mg/kg) [Tanaka K. et al. Arzneimittel Forschung 1992; 42: 935-44]. Using the same animal model, Ceserani et al. (Drugs 1993; 46 Suppl. 1: 48-51) observed that orally and rectally administered nimesulide (ED_{50} range 0.22 to 0.47 mg/kg) displayed more antipyretic potency than

paracetamol (ED50 range 10 to 118 mg/kg) and maintained its potency throughout the observation period (6 to 9 hours after administration of yeast).

After oral administration of nimesulide 50 to 200 mg to healthy adult volunteers, peak serum concentrations of 1.98 to 9.85 mg/L are achieved within 1.22 to 3.17 hours. Compared with values obtained with oral drug administration, peak serum concentrations are slightly lower (2.14 to 2.32 mg/L) and are achieved more slowly (3 to 4.58 h) after rectal administration of nimesulide 100 and 200 mg. Oral drug absorption is nearly complete and concomitant administration of food may decrease the rate, but not the extent of absorption of nimesulide. The drug is extensively bound (99%) to plasma proteins and has an estimated apparent volume of distribution of 0.19 to 0.35 L/kg following oral administration.

Nimesulide is extensively metabolised (1 to 3% of a dose is excreted unchanged in the urine) to several metabolites which are excreted mainly in the urine (≈ 70%) or the faeces (≈ 20%). The drug is almost completely biotransformed into 4-hydroxy-nimesulide in both free and conjugated forms and this metabolite appears to contribute to the anti-inflammatory activity of the compound. Peak concentration of 4-hydroxy-nimesulide ranged from 0.84 to 3.03 mg/L and were attained within 2.61 to 5.33 hours after oral administration of Nimesulide 50 to 200 mg to healthy adult volunteers. The elimination half-life of 4-hydroxy-nimesulide ranges from 2.89 to 4.78 hours and is generally similar to or slightly higher than that of the parent compound (1.56 to 4.95 h).

The pharmacokinetic profile of nimesulide is not significantly altered in children, elderly volunteers and patients with moderately impaired renal function [creatinine clearance 1.8 to 4.8 L/h (30 to 80 ml/min)]. Slight accumulation of 4-hydroxy-nimesulide was noted in patients with moderate renal impairment; however, the clinical significance of this finding is unknown.

Clinical studies have established the analgesic, anti-inflammatory and antipyretic effectiveness of orally (mostly 200 mg/day) or rectally (400 mg/day) administered nimesulide in the treatment of a variety of painful inflammatory conditions, including those associated with osteoarthritis, oncology, postoperative trauma, sports injuries, ear, nose and throat disorders, dental surgery, bursitis/tendinitis, thrombophlebitis, upper airways inflammation and gynaecological disorders. In these indications, nimesulide is more effective than placebo and is at least as effective as therapeutic dosages of other NSAIDs, including piroxicam, ketoprofen, naproxen, etodolac, mefenamic acid, diclofenac, niflumic acid, fentiazae, feprazone and flurbiprofen. Nimesulide therapy was characterised by a rapid onset of analgesia and symptomatic relief in studies where as significant difference in clinical efficacy between active treatment was observed. However, most of these studies evaluated small numbers of patients and were probably too small to identify any small differences in effectiveness.

In children, nimesulide suspension, granules and suppositories are more effective than placebo and are at least as effective as paracetamol,

diclofenac, naproxen, lysine acetylsalicylate, mefenamic acid, ketoprofen and dipyrone in reducing in pain, inflammation and fever associated with respiratory tract infection, postoperative pain and musculoskolotal injury. Nimesulide has been well tolerated by both young and elderly adults and children in 2 large postmarketing surveillance surveys. As with other NSAIDs, the most common adverse effects are gastrointestinal disturbances (epigastralgia, heartburn, nausea, diarrhoea and vomitings 5.1 to 8.5% of patients), dermatological reactions (rash, pruritus; 0.2 to 0.6%) and central nervous system effects (dizziness, somnolence, headache; 0.3 to 0.4%). Withdrawal rates associated with short term (up to 30 days) nimesulide treatment range from 1.1 to 2.2% in adult, elderly and paediatric patients.

Available data indicate that the gastrointestinal tolerability of nimesulide in adults and children is similar to that of other NSAIDs. The rate of endoscopically verified gastroduodenal irritation with nimesulide appears to be similar to that with placebo and diclofenac and less than that with indomethacin. The drug is well tolerated by most patients intolerant of aspirin and/or other NSAIDs and by patients with asthma.

The literature surveys shows that different dosage forms reported for nimesulide are tablets, granules, suppositories and suspension (Drugs 48 (3): 431-454, 1994) and lately our group has patented transdermal (US Pat. No. 5688829) and intramuscular injection (US Pat. No. 5716609) formulations. The reported dosage forms have to be administered twice-a-day based on biological half life of nimesulide. The usual oral/rectal dosage of nimesulide in

adults is 100 to 200 mg twice daily whereas, in children 5 mg/kg/day divided into 2 or 3 daily doses.

Thus, it is desirable to have once-a-day dosage form for nimesulide particularly for treatment of chronic diseases like arthritis. The once-a-day dosage form is expected to significantly increase the dosing convenience and patient compliance. However, controlled release once-a-day dosage form of nimesulide have not been reported so far. By expenditure of considerable intellectual effort and careful experimentation we have found out that nimesulide can be formulated into a controlled release once-a-day dosage form.

SUMMARY OF THE INVENTION

A controlled release composition of nimesulide is disclosed in the invention.

The composition in accordance with present invention comprises a controlled release pharmaceutical composition of Nimesulide which comprises nimesulide as an active drug from 5% to 95% w/w of the composition, one or more sustaining materials from 2% to 95% w/w of the composition and pharmaceutical excipients from 0% to 90% w/w of the composition.

Preferably the composition in accordance with the present invention comprises nimesulide as an active drug from 20% to 70% w/w of the composition, one or more sustaining materials from 5% to 65% w/w of the

composition and pharmaceutical excipients from 10% to 70% w/w of the composition.

More preferably the composition in accordance with the present invention comprises nimesulide as an active drug from 40% to 60% w/w of the composition, one or more sustaining materials from 8% to 20% w/w of the composition and pharmaceutical excipients from 30% to 60% w/w of the composition.

DETAILED DESCRIPTION OF INVENTION

In accordance with the present invention there is disclosed a controlled release composition of Nimesulide.

The composition in accordance with present invention comprises a controlled release pharmaceutical composition of Nimesulide which comprises nimesulide as an active drug from 5% to 95% w/w of the composition, one or more sustaining materials from 2% to 95% w/w of the composition and pharmaceutical excipients from 0% to 90% w/w of the composition.

Preferably the composition in accordance with the present invention comprises nimesulide as an active drug from 20% to 70% w/w of the composition, one or more sustaining materials from 5% to 65% w/w of the composition and pharmaceutical excipients from 10% to 70% w/w of the composition.

More preferably the composition in accordance with the present invention comprises nimesulide as an active drug from 40% to 60% w/w of the composition, one or more sustaining materials from 8% to 20% w/w of the composition and pharmaceutical excipients from 30% to 60% w/w of the composition.

The sustaining materials are selected from the group cellulose and cellulose derivatives, waxes, carbomers, polyalkylene polyols, polycarbophils, methacrylate acid derivatives, gelatins, gums, polyethylene oxides.

The sustaining materials comprise materials which are non-toxic and pharmaceutically acceptable. These may be natural, semi-synthetic, synthetic or man-modified. Suitable materials include cellulose and cellulose derivatives like microcrystalline cellulose, methyl cellulose, ethyl cellulose, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, cellulose acetate phthalate, cellulose acetate, cellulose acetate butyrate, cellulose acetate propionate, cellulose acetate trimellitate, cellulose carboxymethyl ethers and their salts, hydroxypropyl methylcellulose phthalate , hydroxypropyl methylcellulose acetate succinate.

Polyethylene; Polyquaternium-1; Polyvinyl acetate (homopolymer); Polyvinyl acetate phthalate; Propylene glycol alginate; PVM/MA copolymer; PVP/ dimethiconylacrylate/polycarbamyl/polyglycolester;PVP/dimethylaminoethylm ethacrylate copolymer; PVP/dimethylaminoethylmethacrylate/polycarbamyl polyglycol ester; PVP/polycarbamyl polyglycol ester; PVP/ VA copolymer

Lanolin and lanolin derivatives, glyceryl monostearate, stearic acid, paraffins, beeswax, carnauba wax, Tribehenin.

Polyalkylene polyols like polyethylene glycols.

Gelatin and gelatin derivatives.

Alginates. Carbomers. Polycarbophils.

Methacrylic acid copolymers.

Carrageenans, pectins, chitosans, cyclodextrins, lecithins.

Natural and synthetic gums containing galactomannans like xanthan gum, tragacanth, acacia, agar, guar gum, etc.

Pharmaceutical excipients as used in the composition are selected from the group of excipients generally used by persons skilled in the art e.g. fillers, bulking agent, colourants, stabilizers, preservatives, lubricants, glidants, chelating agents and the like.

Preferably the composition also comprises release modifiers. Such release modifiers are selected from the groups wetting agents, solubilizers, surfactants, plasticizers, solvents, pore formers, pH modifiers and tonicity adjusting agents.

Suitable example of such ingredients include :

Reaction products of natural and hydrogenated vegetable oils and ethylene glycol e.g. polyoxyethylene glycolated natural or hydrogenated castor oil such as those available under the trade name Cremophor.

Other suitable products include polyoxyethylene sorbitan fatty acid esters e.g. of the type available under the trade name TWEEN.

Polyoxyethylene fatty acid esters e.g. MYRJ and CETIOL HE.

Polyoxyethylene polyoxypropylene copolymers e.g. PLURONIC and Polyoxyethylene polyoxypropylene block copolymers e.g. POLOXAMER.

Dioctylsodiumsulfosuccinate, sodium lauryl sulphate.

Propylene glycol mono- and di- fatty acid esters e.g. MIGLYOL 840.

Bile salts e.g alkali metals salts e.g. sodium taurocholate.

Polyethylene glycols, propylene glycol, triacetin, diacetin, diethyl phthalate, dibutyl phthalate, castor oil, triethyl citrate, dibutyl sebacate.

Sodium chloride, potassium chloride, lactose, mannitol, sucrose, sorbitol.

Sodium hydroxide, potassium hydroxide, sodium bicarbonate, sodium citrate, citric acid, hydrochloric acid, lactic acid, tartaric acid, malic acid.

The calculation of dose of nimesulide for once-a-day controlled release dosage form was done on the basis of its pharmacokinetic parameters using

the following equation :

$$\text{Dose} = C_P \times V_d \times K_{el} \times T$$

C_P = Effective plasma concentration, 3.0 mg/L

V_d = Apparent Volume of distribution, 15.6 L

K_{el} = Elimination Rate constant, 0.166 h^{-1}

T = Desired Duration of action, 24 hrs

Example 1 Controlled release matrix tablet type

(i) Nimesulide	-	200 mg
(ii) Lactose	-	73 mg
(iii) Hydroxypropylmethyl Cellulose	-	70 mg
(iv) Magnesium Stearate	-	3.5 mg
(v) Purified Talc	-	3.5 mg

Blend (i), (ii), (iii), (iv) and (v) after sifting through mesh no. 30 (BSS). Compress into tablets.

The results of Dissolution Release Profile of Nimesulide CR Tablets based on example 1 are given below :

Table 1

Time	% Release	SD
30 mins.	4.2	± 1.36
1 hr	7.9	± 1.02
2 hrs	16.4	± 1.74

3 hrs	25.8	± 1.28
4 hrs	34.2	± 1.71
6 hrs	50.8	± 2.44
8 hrs	65.9	± 1.86
10 hrs	74.9	± 0.97
12 hrs	85.8	± 2.34
14 hrs	93.5	± 2.49
16 hrs	96.7	± 2.16
18 hrs	97.1	± 1.08
19 hrs	98.8	± 1.32

The dissolution profile as given in table 1 of the nimesulide sustained release tablet should not be construed to limit the scope of the invention. Variations to the dissolution profile can be possible depending upon the dosage requirements without departing from the spirit of the invention.

Example 2 - Extended release membrane diffusion controlled tablet type

(i) Nimesulide	-	200 mg
(ii) Microcrystalline Cellulose	-	60 mg
(iii) Lactose	-	60 mg
(iv) Maize Starch	-	10 mg
(v) Purified Talc	-	3.5 mg
(vi) Ethyl Cellulose (As Aqueous Dispersion)	-	10 mg
(vii) Polyethylene Glycol	-	3.5 mg

Blend (i), (ii) and (iii) and granulate with starch paste and dry the granules. Sift through mesh no. 22 (BSS). Lubricate with Talc. Compress into tablets.

Coat the tablets . Ethyl Cellulose using Polyethy' e Glycol as a channel former.

Example 3 Sustained release bead type

(i) Non – Pareil Beads	-	347 mg
(ii) Nimesulide	-	200 mg
(iii) Mannitol	-	30 mg
(iv) Lactose	-	30 mg
(v) Polyvinyl Pyrrolidone	-	20 mg
(vi) Purified Talc	-	15 mg
(vii) Ethyl Cellulose	-	7 mg
(viii) Diethyl Phthalate	-	1.4 mg

Coat the non-pareil beads with blend of (ii), (iii) and (iv) using (v) as a binder in a conventional or fluidized bed coater. Talc may be dusted onto the beads. Final coating is given with Ethyl Cellulose using (viii) as plasticizer.

Example 4 Osmotically controlled constant release type device

Upper Layer

(i) Nimesulide	-	200 mg
(ii) Sodium Hydroxide	-	15 mg
(iii) Lactose	-	34 mg
(iv) Sodium Chloride	-	30 mg
(v) Polyvinyl Pyrrolidone	-	6 mg
(vi) Polyethylene Oxide	-	1.5 mg

Lower Layer

(vii) Polyethylene Oxide	-	22 mg
(viii) Carbomer 934P	-	1.2 mg
(ix) Hydroxypropylmethyl Cellulose	-	1.8 mg
(x) Sodium Chloride	-	20 mg
(xi) Alcohol	-	q.s (Lost in processing)

Semi-permeable Coat

(xii) Cellulose Acetate	-	30 mg
(xiii)Triacetin	-	1 mg
(xiv) Acetone	-	q.s (Lost in procesing)
(xv) Water	-	q.s (Lost in processing)

Blend finely powdered (i), (ii), (iii), (iv) and (vi). Granulate with aqueous solution of (v). Granulate the blend of (vii), (ix) and (x) with dispersion of (viii) in alcohol. Compress the two granulates into bilayer tablets and coat with the dispersion of (xii) and (xiii) in aqueous acetone. Finally, drill a hole in the drug layer (Upper layer) through which the drug is released in a controlled fashion due to osmotic pressure.

The results of Dissolution Release Profile of Nimesulide CR Tablets based on example 4 are given below :

Table 2

Time	% Release	SD
2 hours	5.16	± 0.53
4 hours	16.75	± 1.68
6 hours	34.90	± 2.26
8 hours	45.75	± 2.26

10 hours	56.00	± 4.36
12 hours	67.85	± 4.40
14 hours	79.16	± 5.03
16 hours	90.25	± 3.68
18 hours	101.16	± 3.53

Example 5 Coated capsule type

(i) Nimesulide	-	200 mg
(ii) Microcrystalline Cellulose	-	88.4 mg
(iii) Lactose	-	70 mg
(iv) Polyvinyl Pyrrolidone	-	7 mg
(v) Magnesium Stearate	-	3.9 mg
(vi) Ethyl Cellulose	-	20 mg
(vii) Polyethylene Glycol	-	0.7 mg
(viii) Alcohol : Dichloromethane (1 : 2)	-	q.s (Lost in processing)
(ix) Empty Gelatin Capsule (Size '1')		

Blend (i), (ii), (iii), (iv) and (v) and fill into empty gelatin capsule size '1'. Coat the capsules with dispersion of (vi) and (vii) in (viii).

Example 6 pH dependent delayed release type

(i) Nimesulide	-	100 mg
(ii) Microcrystalline Cellulose	-	150 mg
(iii) Lactose	-	76 mg
(iv) Polyoxyl 40 Hydrogenated Castor Oil	-	7 mg
(v) Polyvinyl Pyrrolidone	-	10 mg

(vi) Magnesium Stearate	-	3.5 mg
(vii) Purified Talc	-	3.5 mg
(viii) Cellulose Acetate Phthalate	-	28 mg
(ix) Diethyl Phthalate	-	2 mg
(x) Water	-	q.s (Lost in processing)
(xi) Alcohol : Dichloromethane (1:2)	-	q.s (Lost in processing)

Granulate the blend of (i), (ii) and (iii) with solution of (iv) and (v) in water. Blend the granules with (vi) and (vii). Compress into tablets. Coat with the dispersion of (viii) and (ix) in (xi).

Example 7 Timed release bead type

(i) Nimesulide	100 mg	100 mg	100 mg
(ii) Microcrystalline Cellulose	200 mg	200 mg	200 mg
(iii) Lactose	50 mg	42 mg	35mg
(iv) Polyvinyl Pyrrolidone	10 mg	10 mg	10 mg
(v) Water	q.s	q.s	q.s
(vi) Ammonio Methacrylate Copolymer Type B (Eudragit RS)	10 mg	18 mg	25 mg
(vii) Diacetin	0.5 mg	0.5 mg	0.5 mg
(viii) Water : Acetone (1:9)	q.s	q.s	q.s

The foregoing examples are illustrative embodiments of the invention and are merely examplary. A person skilled in the art may make variations and

modification. Without departing from the spirit and scope of the invention. All such modifications and variations are intended to be included within the scope of the invention as discuss in this specifications.

We claim :

1. A controlled release pharmaceutical composition of Nimesulide which comprises nimesulide as an active drug upto 99% w/w of the composition, one or more release controlling materials from 0.1% to 99% w/w of the composition and pharmaceutical excipients from 0% to 90% w/w of the composition.

2. A controlled release pharmaceutical composition of nimesulide as claimed in claim 1 which comprises nimesulide as an active drug from 20% to 70% w/w of the composition, one or more sustaining materials from 5% to 65% w/w of the composition and pharmaceutical excipients from 10% to 70% w/w of the composition.

3. A controlled release pharmaceutical composition of nimesulide as claimed in claim 1 which comprises nimesulide as an active drug from 40% to 60% w/w of the composition, one or more sustaining materials from 8% to 20% w/w of the composition and pharmaceutical excipients from 30% to 60% w/w of the composition.

4. A controlled release pharmaceutical composition of nimesulide as claimed in claim 1 to 3 wherein the sustaining materials are selected from the group cellulose and cellulose derivatives, waxes, carbomers, polyalkylene polyols, polycarbophils, methacrylate acid derivatives, gelatins, gums, polyethylene oxides and alike.

5. The composition as claimed in claim 1 which further comprises release modifiers.

6. A process for the manufacture of controlled release compositions of nimesulide which comprises mixing together under conventional

con ns of temperature and pressure imesulide as an active drug upto 99% w/w of the composition, one or more release controlling sustaining material from 0.1% to 99% w/w of the composition and pharmaceutical excipients 0% to 90% w/w of the composition.

7. A controlled release pharmaceutical composition of Nimesulide substantially as herein described with reference to foregoing description and the accompanying examples.

8. A process for the manufacture of controlled release compositions of nimesulide substantially as herein described with reference to foregoing description and accompanying examples.

Dated this 28th day of September, 1999.

Sharadeva

(SHARAD VADEHRA)
of KAN AND KRISHME
ATTORNEY FOR APPLICANTS